REMARKS:

The Examiner has cited formal objections to the drawings as listed on the PTO Form 948 accompanying a prior Office Action. As the Examiner has previously stated that the drawings are acceptable for examination purposes, no amended drawings are presented herewith. Instead, formal drawings will be filed upon allowance of the application.

The Examiner rejected Claims 1-18 under 35 U.S.C. Sec. 102(e) as anticipated by Dunkel, U.S. Patent No. 5,572,125. After carefully reviewing the referenced patent, the applicant respectfully submits that there are at least two important differences between the invention claimed in the present application and that described in the Dunkel reference. Those differences include: (1) Dunkel's patent does not, indeed it cannot, describe a method for characterizing the three-dimensional structure of a large molecule as claimed by the applicant; and (2) While Dunkel's invention discusses the use of "complex molecules," it has nothing to do with the applicant's claimed method of electrospray ionization mass spectrometry of molecule complexes.

As described throughout his patent, Dunkel's invention clearly is limited to a method for the correction of various types of signal

distortion found in Fourier Transform Nuclear Magnetic Resonance Spectrometers. Indeed, his application of computer simulations using Monte Carlo computational methods is directed specifically toward the improvement of signal-to-noise ratios for the purpose of improving the spectra obtained.

In contrast, the present invention is based on two completely independent systems, one experimental and one computational, linked in such a way as to provide a 3-D, quantum mechanically correct, computer molecular model or image that, through computational methods, reveals the conformation of a protein (or other type of large molecule). Therefore, in the broadest sense, this invention represents the initial development of a system combining experimental and computational methods allowing for experimental data to be presented as a computer synthesized, chemically correct molecular image. In other words, the present invention describes a method for characterizing an experimental 3-D structure of a molecule being analyzed. Thus, the applicant's invention is completely unrelated to Dunkel's method for improving signal-to-noise ratios using Fourier transformation methods.

Turning to the specific concerns listed in the Office Action, the Examiner begins by stating that "[Dunkel's] method includes the steps of mixing molecules to form a mixed solution of complex

molecules for analysis." While this may indeed be the case, both independent claims (1 and 7) of the present application, in contrast, specifically recite "mixing a small molecule with a large molecule...to form a large molecule-small molecule complex." In other words, both claims 1 and 7 specifically recite molecule complexes, not "a mixed solution of complex molecules." Since a "complex molecule" is not the same as a "molecule complex," Dunkel cannot anticipate the present invention as claimed.

With further regard to claim 1, the Examiner then states that Dunkel's method involves "performing electrospray ionization mass spectroscopy to obtain spectroscopic data of the molecule complexes." Yet, despite the Examiner's general citation of several columns and sections, there is not a single mention of electrospray ionization mass spectrometry anywhere in Dunkel's patent. Thus, it is respectfully submitted that Dunkel does not describe the use of this type of spectrometry in his method. But even if he did, Dunkel's patent only deals with the correction of spectrum data, not the characterization of a 3-D structure based on the spectroscopic analysis of large and small molecule complexes as described and claimed by the applicant.

Lastly, the Examiner states that claim 1 is anticipated because Dunkel's method involves "repeating the procedure steps above if [sic] necessarily in order to obtain a good resolution for characterizing [the] 3-D structure [of] molecules." This assertion by the Examiner is perplexing, as nowhere does Dunkel describe or suggest the characterization of the three-dimensional structure of large molecules by his method. In fact, the only "3-D" aspect of Dunkel's method is displayed in Figs. 18a-f, 21a-f, and 24a-d, which show three-dimensional graphs of spectral data, not three dimensional structures of large molecules. These graphs of spectral date have absolutely no connection to a computationally synthesized, quantum mechanically correct, computer image of a molecule.

If anything, Dunkel's method is only useful for correctly predicting atom connectivity, not how the atoms are arranged in space. As one skilled in the chemical arts readily recognizes, a protein's (or other large molecule's) 3-D structure cannot be obtained solely from its atom connectivity.

Regarding independent claim 7, Dunkel only discloses a method and/or machine for acquiring, analyzing and correcting spectral and imaging data for the sole purpose of improving signal-to-noise values, thus yielding spectra with improved signal. Moreover, Dunkel's computer simulations are based entirely on

Monte Carlo simulation with only unidirectional feedback (see col. 37, line 29 to col. 42, line 43).

Furthermore, as discussed above for claim 1, the Examiner's reliance on the disclosure in Dunkel of a "mixed solution of complex molecules" to anticipate the present invention is clearly based on a misreading of a the "mixing a small molecule with a large molecule...to form a large molecule-small molecule complex" limitation found in claim 7. Again, Dunkel's invention can provide no insight into, nor does it suggest any possible way of elucidating, the three-dimensional structure of large molecules (and especially not 3-D structures bases on spectrometry of large molecule/small molecule complexes).

Furthermore, Dunkel does not anticipate claim 7 based on, as stated by the Examiner, "bonding strength based on spectroscopic data in simulation model which would include bonding strength, bond energy, etc., as known for those skilled in the spectroscopy analysis." Bonding strength and bond energy cannot be obtained from the method described by Dunkel. This is because these thermodynamic properties must be calculated using suitable, specialized programs based on ab initio or semi-empirical quantum mechanical methods (all of which are outlined in the present application but are not even mentioned by Dunkel).

In fact, Dunkel's use of the stochastic Monte Carlo method would not allow the calculation of thermodynamic properties, even if Dunkel wished to use the Monte Carlo method for something other than noise reduction. In addition, Dunkel does not anticipate, as stated by the examiner, "data model being corrected to improve a selected residue on the molecule, and repeating the procedure steps above if necessarily in order to obtain a good resolution for characterizing 3-D structure molecules." First, a residue is a specific chemical term used to describe one amino acid in a polypeptide chain or protein. Dunkel makes no mention of 'residues', and even if he had, his invention would only refer to the linear connectivity (not 3-D structure) of these residues in a chain of amino acids.

Dunkel also does not disclose "characterizing 3-D structure molecules." Dunkel is merely using an n-dimensional mathematical model, based on estimates, to simulate a signal from which the noise may be extracted. Thus, a 3-D mathematical model, as described by Dunkel, has nothing to do with the 3-D structure or 3-D computer image of a molecule.

In view of the clear differences between Dunkel and both independent claims of the present invention, the applicant respectfully submits the claim 1 and claim 7 are not in any way anticipated (or rendered obvious). Since each independent claim

is clearly distinguishable from Dunkel, each dependent claim would also be so distinguished. Therefore, the applicant submits that all dependent claims would also be allowable as presently written.

However, in the interest of further clarifying the present invention, the following discussion addresses the Examiner's reasons for rejection of the dependent claims.

Regarding claims 2 and 8, Dunkel's invention uses a "computerized data processing system including plurality of means for performing steps, such as processing means for computing error data, phase shift data, etc., memory for storing computational results," solely for improving signal-to-noise ratios. This is accomplished by reducing noise through the specific application of Fourier transformation methods, resulting in an improved spectrum. As mentioned previously, this data correction method has nothing to do with the present invention, which produces an accurate three-dimensional representation of a molecule through the use of "feedback modeling."

In fact, the applicant's method of "feedback modeling" would allow for the elucidation of new data not obtainable from the spectra alone, by, for example, the application of quantum mechanically accurate computer modeling programs. Dunkel is not

able to use his invention to provide new data not already contained in the Fourier transformation acquisition; he can only reduce the noise found in existing data. Moreover, while the modeling programs referred to in the present application have been well documented in the literature, they have not been used previously in a feedback loop as described. Thus, the present invention is clearly new.

With further regard to claim 2, the Examiner states that "Dunkel also anticipates simulating the model to predict error and correct the model using feedback loop as claimed." Again, Dunkel's use of Monte Carlo methods represent a stochastic approach for the purpose of eliminating noise to produce an improved spectrum. In fact, he is not "simulating the model;" he is simulating the experimental system, based on initial estimates. In other words, the feedback loop used by Dunkel is based on feedback from the simulation to the experimental data, which is, in effect, a unidirectional feedback. Dunkel does not allow for any manipulation or modification of the chemical system being analyzed prior to, during, or after the simulation.

In contrast, the present invention uses a bi-directional feedback, allowing for computer-controlled manipulation of experimental parameters, and allowing for chemical changes to be

made in the chemical system during analysis. This results in new experimental data that is returned to the computational system for further computation, the results of which control changes in the experimental chemical system, which allows for the elucidation of new data (and not merely a reduction in noise) not obtainable by either system independently.

Regarding claims 3-6, the Examiner states that the "variety of complex molecules such as cholesterols, proteins and protein complex structures" anticipates the applicant's claims. However, the Examiner again fails to recognize that molecule complexes, not "complex molecules" are claimed in the present invention. Thus, the fact that the Examiner considers cholesterol or a protein to be a "complex molecule" is irrelevant to present invention. Moreover, what exactly the Examiner means by "protein complex structures" is mysterious, for nowhere does Dunkel disclose the ability to use his invention with proteins or complexes of proteins with small molecules. In fact, all of Dunkel's examples and data involve small bioorganic molecules, which includes cholesterol, Na_2MoO_4, conotoxin, and 1,1-dimethyltetralin.

Moreover, Dunkel's only reference to proteins is with regard to protein sequencing (col. 33, lines 59-62), which cannot be construed to mean whole proteins as protein sequencing invariably

involves the analysis of a series of small polypeptide fragments. Besides, protein sequencing provides only the linear connectivity of amino acids, not the 3-D conformation. Therefore, Dunkel's reference to proteins or "polymers" does not imply that he can apply his method to whole proteins, DNA, RNA or other large biomolecules. This is supported by the fact that (1) Dunkel uses a 500 MHz NMR spectrometer (col. 21, lines 30-40), which would not be sufficient for the analysis of a protein such as Cytochrome c (the molecule characterized by the applicant); and (2) the largest molecule identified by Dunkel, conotoxin, is a small (22 amino acid) polypeptide, not a protein.

Regarding claims 9-15, again the Examiner fails to recognize that a molecular complex has an entirely different meaning from "complex molecules." Once more, Dunkel's invention is directed toward the reduction of noise to improve a data signal using Fourier transformation analysis and Monte Carlo simulations. Even if one could predict a 3-D structure with Dunkel's method as the Examiner suggests, only very small structures could be inferred, and then only through the application of basic chemical principles (none of which are described by Dunkel).

However, a likely 3-D structure cannot be inferred using basic chemical principles when large molecules or macromolecules, such as proteins, are being described. Instead, the 3-D structure of

proteins must be determined using other experimental methods, none of which are mentioned by Dunkel. Thus, the present invention is clearly distinguishable from Dunkel because it describes and specifically claims a method for characterizing the 3-D structure of a large molecule.

Regarding claim 16, the examiner states that, "Dunkel anticipates bonding strength or binding energy of complex molecules such [that?] energy required to create a bond which would inherently include heat of formation in the complex large molecules claimed." The applicant respectfully disagrees. Dunkel does not make any statements regarding bonding strength, binding energy, or heat of formation. Nowhere in his patent are these thermodynamic properties inferred nor calculated. Indeed, Dunkel only mentions "bond signals," i.e., spectral data, which have absolutely no connection to these thermodynamic properties.

Finally, regarding claims 17-18, the Examiner's interpretation of Dunkel's disclosure as describing a "plurality of complex molecules which would include and not limited to the claimed invention," is not correct. Again, a "plurality of complex molecules" has absolutely no connection to a molecular complex, which is key in understanding the present invention. Furthermore, Dunkel makes no disclosure regarding protein/small

molecule complexes.

In summary, unlike the claims of the present application, there is no disclosure or suggestion in Dunkel of a method that elucidates the 3-D structure of macromolecules, proteins, DNA, or RNA based on spectrometry of molecular complexes resulting from the non-covalent interaction of a macromolecule or protein with a small molecule.

In view of the foregoing, the applicant respectfully requests that this case be advanced to allowance. However, if any issue remains that could be resolved by telephonic interview, the undersigned would appreciate the opportunity to do so.

Other than the enclosed check for a petition for a two month extension of time, no fee is believed to be due with this response. Should there be any unforeseen costs, please charge our Deposit Account No. 04-1935.

Respectfully submitted,

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